Brain responses to strong desire to void with synchronous urodynamics in healthy adults: a functional magnetic resonance imaging study based on graph theory

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Abstract

Background

The alternations of brain responses to strong desire to void during a urodynamic study were unclear. The present study aims to identify the functional brain network's topologic property changes evoked by a strong desire to void in healthy male and female adults with synchronous urodynamics using a graph theory analysis.

Methods

The bladders of eleven healthy males and eleven females were filled with a catheter in a specific infusion and withdrawal pattern. The resting-state functional magnetic resonance imaging (fMRI) of the enrolled subjects was scanned under the empty bladder and strong desire to void states. Automated anatomical labeling (AAL) atlas was used to identify the ninety cortical and subcortical regions. Pearson's correlation calculations were performed to establish a brain connection matrix. A paired t-test ($P < 0.05$) and Bonferroni correction were applied to identify the significant statistical differences in topologic properties between the two states, including small-world network property parameters [γ and λ], characteristic path length (L_p), clustering coefficient (C_p), global efficiency (E_{glob}), local efficiency (E_{loc}) and regional nodal efficiency (E_{nodal}).

Results

Significantly, a small-world network property was presented in all subjects. The significantly decreased C_p , L_p , E_{loc} , and increased E_{glob} were detected in the female subjects under the strong desire to void. Notably, the increased E_{nodal} was observed in left the orbital part of middle frontal gyrus and inferior frontal gyrus, right middle temporal gyrus, median cingulate and middle occipital gyrus, and bilateral inferior parietal gyrus, gyrus rectus and supramarginal gyrus. In the male subjects, the increased E_{nodal} presented in right frontal operculum and medial superior frontal gyrus, left supplementary motor area and the bilateral supramarginal gyrus. On the other hand, the significant decreased E_{nodal} in female subjects was detected in the bilateral calcarine fissure and surrounding cortex, lingual gyrus, and fusiform gyrus. The decreased E_{nodal} in male subjects presented in right inferior occipital gyrus and thalamus.

Conclusions

In the study, there were potential gender differences in functional brain network's topologic property alternations in response to the strong desire to void under a repetitive infusion and withdrawal pattern.

1. Background

There are two primary functions for the lower urinary tract, namely storage and voiding. Humans can shift back and forth between the two phases, depend on the coordination of the brain, spinal cord pathway, peripheral nerve, bladder, urinary sphincter, and pelvic floor muscles. Significantly, any interruptions in functional coordination could lead to lower urinary tract dysfunctions (LUTD), manifesting symptoms such as urinary frequency, urgency, incontinence, and dysuria [1]. We implored the urodynamic tests, a well-developed and applied urological clinical profile to assess LUTD. Urodynamic tests [2, 3, 4] was considered an ideal method to estimate both storage and voiding function with a specific transurethral and a transrectal catheters. A strong desire to void is characterized by a quiet crucial sensory parameter tightly related to urinary continence [5]; additionally, it impacts the gait of individuals with multiple sclerosis and urinary disorders and [6, 7]. As reported in a study by Kaynar et al. [8], the highest maximum flow rate and average flow rate are obtained with a strong desire to void, suggesting its influences on the urinary voiding.

Presently, functional magnetic resonance imaging (fMRI) based on blood oxygen level-dependent (BOLD) is being applied to investigate the supraspinal control of the lower urinary tract (LUT) in healthy subjects and patients with LUTD. Likewise, activations in the dorsal pontine, insula, prefrontal cortex, supplementary motor area, and the anterior and the middle cingulate gyrus have been found in healthy subjects [9]. Abnormally activated brain regions and the alternations of functional connections in diseases with LUTD have been reported, including overactive bladder [10, 11], stroke, and multiple sclerosis [12]. Nonetheless, the topologic property changes were barely known. Although different patterns (especially the perfusion speed) of urinary bladder filling were generally considered as the potential influencing factors for the result of urodynamic results, the alternations of brain responses resulting from these patterns were unclear yet.

A series of baseline brain fMRI study concerning a strong desire to void was launched in healthy subjects to determine the central mechanism of the various LUTD in future. In the series, various patterns of urinary bladder filling were involved. In the present article, with a repetitive infusion and withdrawal pattern, the functional brain network's topologic property alternations evoked by a strong desire to void in healthy male and female adults will be respectively reported.

2. Materials And Methods

2.1 Participants and Ethics Statement

Twenty-two healthy participants (11 males and 11 females) between 2017 and 2018 were enrolled. All healthy participants were asked to fill a 3day voiding diary. Notably, the physical tests were satisfactory, and no abnormal medical history existed. The 24-hour urine volume ranged between 1500 to 3000ml. Urination frequency was $\geq$ eight times/day and $\leq$ one time/night with an average urine volume of $\geq$ 200ml/time. No urine leakage. The exclusion criteria included having: (1) LUT symptoms; (2)

neurological diseases or lesion, such as myelitis; (3) multiple sclerosis; (4) traumatic spinal cord injury; (5) tumors, especially pelvic tumors; (6) currently undergoing radiotherapy or chemotherapy; (7) taking medications or other substance which could impact on the nervous system or urinary system; (8); pregnancy test was positive; (9) claustrophobia; and (10) having medical taboo to scanning. These participants signed an informed consent form and the study was executed in accordance with the revised Helsinki Declaration, and the study's ethics approval was provided by the Ethics committee of China Rehabilitation Research Center (IRB: 2017-002-1).

2.2 Image acquisition and preprocessing

All images were acquired on an Ingenia 3.0 Tesla scanner (Philips, Eindhoven, The Netherlands). Before fMRI scans, the subjects were asked to void. Subjects lay supine while wearing headphones. A fixed device was used to limit the motion of patient's head. A 7 Fr double-lumen bladder catheter and a rectal catheter were inserted to monitor vesical pressure and intra-abdominal pressure with a portable urodynamic device (Laborie Medical Technologies, Vermont, United States). The procedure's complete details were explained to the subjects, including closing their eyes and lying awake during scanning without any systematic thoughts. Structural T1 images (3D; repetition time = 7.8ms; echo time = 3.8 ms; and flip angle = 8 degrees) were collected 10mins after voiding. Then a gradient-echo, echo-plane imaging sequence (echo time = 30ms; repetition time = 2000ms; flip angle = 90 degrees; voxel size = $3 \times 3 \times 3.5$ mm) was applied to all volunteers' first resting-state fMRI scans.

The scanning lasted 6mins 14sec, and synchronous urodynamics evaluation was performed during the first resting-state functional brain scanning. After 200ml of 0.9%, sterile saline solution was infused into the subjects' bladder by a syringe; the urinary bladder was filled via four blocks (Fig. 1) with sterile saline solution. The second resting-state for fMRI scans were performed using prior resting-state parameters, while a strong desire to void was reported. The urge to void was evaluated using a visual analog scale (score 0: empty bladder; score 6: strong desire to void; score 8: urge desire to void; score 10: pain), which had been applied in previous researches [13, 14]. Finally, bladder volume was measured after the voluntary elimination into a counting cup.

Standard preprocessing of acquisitions was performed with SPM8 (<https://www.fil.ion.ucl.ac.uk/spm/software/spm8>). The first ten volumes were excluded from functional scans for magnetization equilibration. Slice timing correction, motion correction, the co-register between functional and structural scans, segmentation of structural images, normalization to Montreal Neurological Institute space, resampling with $3\text{mm} \times 3\text{mm} \times 3\text{mm}$ voxel size, spatial smoothing with a 6mm Gaussian kernel, detrending, and filtering with low-pass frequency filter (0.01-0.1Hz) were performed step by step. The data with head horizontal displacement in three-dimensional space > 2 mm and head rotation $> 2^\circ$ would be excluded during motion correction. Finally, nuisance signals resulting from head motion, white matter, cerebrospinal, and the global signal were regressed out.

2.3 Establishment of connection matrix/networks

The functional brain networks were established via graph theory methods, where

nodes represent various brain regions, while edges were modeled as a pairwise connection between nodes. The graph theory analysis was performed using GRETNA 2.0.0 toolbox (<https://www.nitrc.org/projects/gretna/>). Region of interest (ROI), i.e., brain nodes, were initially identified using the automated anatomical labeling (AAL) atlas. The brain was divided into ninety anatomic regions (regions 1-90) using the ALL atlas. Then the time series of the corresponding brain regions were extracted from the preprocessed data. Pearson's correlation calculations were performed to determine the associations between achieving the time series of pairwise different brain regions. Furthermore, a 90×90 brain connection matrix (Fig. 2) was achieved from each subject's data. For normalization, a z-score was calculated with the Fisher r-to-z method. The graph analysis irrelevant or weak functional connections were excluded with proportional network thresholding (sparsity T, 0.05-0.5; intervals, 0.05). When Pearson's correlation coefficient of individual pairs of connections was not greater than T, the corresponding connections were identified and removed. Otherwise, the functional connections were considered to exist. The thresholding methods had been reported in the previous study [15].

2.4 Graph analysis—Network Property Analysis

The twenty-two subjects were divided into the healthy male group and the healthy female group. Small-world properties, global efficiency (E_{glob}), and local efficiency (E_{loc}) were analyzed for the operational data after voiding and the acquired functional scans when subjects strongly desired voiding. The characteristic path length (L_p) and the clustering coefficient (C_p) are significant global metrics. L_p , a parameter estimating the network's integration function, is defined as the average shortest path lengths for all possible pairs of nodes. C_p expresses the density of connection of a node's connection, which measures the network's segregation. The more outstanding C_p is, the denser the connections are. High E_{glob} and E_{loc} in the small-world network ensure the optimal function in segregation and integration. C_p and L_p of the entire functional brain networks were normalized via matching with generated random networks ($n = 100$) for the quantity of the small-world characteristics.

The gamma (γ) and lambda (λ) were obtained from the L_p and C_p of the entire network and random networks ($\gamma = C_{p \text{ real}} / C_{p \text{ rand}}$; $\lambda = L_{p \text{ real}} / L_{p \text{ rand}}$). Sigma (σ , $\sigma = \gamma / \lambda$) was used to describe the small-world coefficient. If $\gamma > 1$, $\lambda \approx \text{one}$, and $\sigma > 1$, the network has small-world properties. E_{glob} was used to estimate the network's communication efficiency and E_{loc} expressed the efficiency of the local subgraph of specific nodes that contains only the direct neighboring nodes. In terms of regional network properties, nodal efficiency (E_{nodal}) evaluating a given node's capacity for information communication with the other nodes was calculated.

2.5 Statistical analyses

For statistical analysis, a paired t-test ($P < 0.05$) and Bonferroni correction between the empty bladder and strong desire to void was applied in both groups to obtain significant differences in small-world topologic property parameters (γ and σ), L_p , C_p , E_{glob} , E_{loc} , and regional E_{nodal} .

3. Results

The resting state fMRI data of eleven males and eleven females were analyzed in the study. A male and a female were excluded for head motion (head displacement > 2 mm and head rotation > 2°). Ten females (mean age: 51.4 years, age range: 35–65 years) and ten males (mean age: 51.6 years, age range: 45–64 years) were available for final statistical analysis (Table 1). There wasn't statistical difference between the both group in the sensory score of visual analog scale. Urodynamic findings showed the stationary and normal urinary storage in all healthy subjects, without detrusor overactivity detected (Fig. 3).

Table 1
The characteristics of the healthy female and male subjects

Characteristics	Females	Males
Numbers	10	10
Age (mean $\pm$ SD)	51.4 $\pm$ 5.9	51.6 $\pm$ 5.4
Education(years)	7.2 $\pm$ 1.6	10.9 $\pm$ 3.7
Mean score of visual analog scale	6.7 $\pm$ 0.9	6.9 $\pm$ 0.8
Bladder volume under strong desire to void (ml)	436.0 $\pm$ 129.7	407.0 $\pm$ 139.1
Bladder diary (72h)		
Frequency/Urgency/Leakage(times)	0	0
Adverse events after the study		
Frequency/Urgency/Leakage(times)	0	0
Dysuria/Urinary retention/hematuria	0	0

3.1 Global functional network properties

After normalizing with random networks, higher C_p ($\gamma > 1$) and L_p ($\lambda \approx 1$) for network sparsity was observed in all subjects under the empty bladder (mean $\pm$ SD, γ in female group: 1.48 $\pm$ 1.95; γ in the male group: 2.00 $\pm$ 2.25; λ in the female group: 0.30 $\pm$ 1.14; λ in the male group: 0.31 $\pm$ 1.14) and strong desire to void state (mean $\pm$ SD, γ in the female group: 1.52 $\pm$ 2.01; γ in male group: 1.55 $\pm$ 2.03; λ in female group: 0.23 $\pm$ 1.10; λ in male group: 0.22 $\pm$ 1.10). Small-world properties ($\sigma > 1$) was detected in both groups under empty bladder (mean $\pm$ SD, σ in the female group: 0.63 $\pm$ 1.59; σ in the male group: 0.94 $\pm$ 1.81) and strong desire to void state (mean $\pm$ SD, σ in the female group: 0.77 $\pm$ 1.70; σ in the male group: 0.86 $\pm$ 1.73). There were no significant differences in the small-world coefficient (σ , $P > 0.05$) between the states in the two groups. Compared with the empty bladder state, the significant decreased C_p , L_p , E_{loc} , and increased E_{glob} ($P \leq 0.05$) were detected in the female group under a strong desire to void (Fig. 4). In the male group, significant decreased E_{loc} in the state with a strong desire to void. There were no statistical differences between the two states in C_p , L_p , and E_{glob} . ($P > 0.05$) (Fig. 5).

3.2 Regional nodal efficiency of functional brain networks

In the female group, the significant increase in E_{nodal} ($P < 0.05$ after FDR correction) under a strong desire to void state was observed in the following brain regions compared to the empty bladder: (1) left prefrontal gyrus (Frontal_Inf_Oper_L and Frontal_Med_Orb_L); (2) bilateral gyrus rectus (Rectus_L and Rectus_R); (3) median cingulate and paracingulate gyrus (Cingulum_Mid_R); (4) middle occipital gyrus (Occipital_Mid_R); (5) bilateral inferior parietal gyrus (Parietal_Inf_L and Parietal_Inf_R); (6) bilateral supramarginal gyrus (SupraMarginal_L and SupraMarginal_R); and (7) Middle temporal gyrus (Temporal_Pole_Mid_R). Furthermore, a significant decrease in E_{nodal} was detected in the bilateral calcarine fissure and surrounding cortex (Calcarine_L and Calcarine_R), lingual gyrus (Lingual_L and Lingual_R), and fusiform gyrus (Fusiform_L and Fusiform_R) (Fig. 6a, Fig. 6b).

Notably, a significant increase in E_{nodal} ($P < 0.05$ after FDR correction) in the state with a strong desire to void was detected in the right frontal operculum (Rolandic_Oper_R), left supplementary motor area (Supp_Motor_Area_L), medial superior frontal gyrus (Frontal_Sup_Medial_R), and the bilateral supramarginal gyrus (SupraMarginal_L and SupraMarginal_R). However, a decrease in E_{nodal} was observed in the inferior occipital gyrus (Occipital_Inf_R) and thalamus (Thalamus_L) (Fig. 6c, Fig. 6d).

4. Discussion

In the past two decades, more than twenty studies addressed brain fMRI findings on urinary bladder control while simultaneous healthy females and males were barely enrolled as subjects or healthy controls in these studies [16]. In the study, the data of the healthy female group and male group were obtained and analyzed under the same scanning parameters, respectively. The differences of brain topologic property alternations evoked by the strong desire to void state may provide the understanding for the central-LUT control mechanism in healthy women and men.

4.1 Global graph metrics

In the study, the repetitive infusion and withdrawal pattern was used to activate the regions related to LUT control. Small-world network properties were observed in the empty bladder and a strong desire to void state in both groups. High C_p and low L_p are the small-world architecture's outstanding characteristics, which are optimized for information processing. Balanced functional integration and segregation were observed in the small-world architecture according to previous general assumptions. High E_{glob} and E_{loc} were detected in the small-world networks, which demonstrated higher efficiency in global and local information communication than the regular network (with low E_{glob} and high E_{loc}) and the random network (with high E_{glob} and low E_{loc}).

Although the small-world properties were detected in both states, the significantly decreased C_p and E_{loc} were observed in the females provoked by a strong desire to void compared with the empty bladder state, which revealed the lower capacity in local information processing and the decreased efficiency in local

information transmission. The significantly decreased L_p and increased E_{glob} in globally connected graphs suggested the higher capacity in the information processing and higher efficiency in global information communication transmission and a better functional integration in female group.

In the male group, the decreased E_{loc} was observed under the strong desire to void state compared with the empty bladder state, revealing the lower efficiency in local information transmission. The results implied the decreased tendency of functional segregation in the male group. There were no statistical differences of C_p , L_p and E_{glob} between the both states.

4.2 Regional nodal metrics

In the female group, the significant increased E_{nodal} under a strong desire to void state was detected in left inferior frontal gyrus and the orbital part of middle frontal gyrus, right median cingulate gyrus, middle occipital gyrus and middle temporal gyrus, and bilateral gyrus rectus, inferior parietal gyrus and supramarginal gyrus. In the male group, the increased E_{nodal} presented in right frontal operculum and medial superior frontal gyrus, left supplementary motor area and the bilateral supramarginal gyrus. The significant decreased E_{nodal} in female group was detected in the bilateral calcarine fissure and surrounding cortex, lingual gyrus, and fusiform gyrus. The decreased E_{nodal} in male group presented in right inferior occipital gyrus and thalamus.

Present clinical human trials and animal experiments [17, 18, 19] have showed that there was a notable voiding reflex between the bladder and the midbrain periaqueductal gray (PAG). During the bladder storage, the afferent filling sensory signals resulted in bladder distension until the volume threshold in PAG was exceeded. The voiding reflex was provoked to relax the urethral sphincter and contract bladder detrusor, while voiding. Urinary bladder storage restarted when it was empty. In fact, the higher central mechanism works in the entire bladder filling and voiding process.

The prefrontal cortex (PFC) is crucial for the LUT control. PFC involved in human personality, decision-making, and social behavior. Significantly, the cortex has been presumed to control voluntary action, including deciding to void [20]. In a previous research [21], as the urinary bladders were passively infusion, healthy female brain responses to larger bladder volume increased in the orbitofrontal cortex. But in patients with overactivity bladder and poor bladder control had weaker responses in the region. The lateral PFC concerns cognition, especially in work memory [22]. Structural MRI has demonstrated the failure to postpone voiding due to the lateral PFC lesion in adult males and females [23]. Children with monosymptomatic nocturnal enuresis manifested abnormal resting-state connectivity in the region [24]. In the study, the regional E_{nodal} in lateral PFC where left opercular part of inferior frontal gyrus located indeed increased compared with the empty bladder in female group. Early Positron-emission tomography (PET) and single photon emission computed tomography (SPECT) studies reported the activation in the bilateral inferior frontal gyrus, but the evidences were absent in male fMRI [9] and the increased E_{nodal} only presented in female subjects in the study. An increased regional E_{nodal} at medial PFC was detected in both groups. Medial PFC was an essential part of default mode network (DMN) [25]. Interoceptive and

spatial representations of the body were integrated into DNM, including the bladder sensory [26]. When it came to self-awareness and self-reflection under a resting state, DNM was activated. Additionally, the region works in the cognitive process, regulating emotion, and sociability [27]. Medial prefrontal gyrus lesions were found to result in relatively short-term incontinence in adults. Nevertheless, the white-matter lesion in the medial PFC also led to long-term urinary bladder dysfunction [28]. And a fMRI research showed the region was deactivated under the full urinary bladder in patients with urgency incontinence [29]. The gyrus rectus was an essential region of the medial prefrontal network, which mediated the interaction between the visceromotor centers and the prefrontal sensory signals via the hypothalamus's descending pathway and the brainstem [30]. The ventromedial PFC was proved to connect with the limbic system and other brain regions, which determine its vital roles in LUT control.

The cingulate gyrus as a component of the limbic system was known for multiple functions such as the mediation of emotional and autonomic responses to external stimuli, and processing the information from the bladder to maintain urinary continence and impact on the urge to void [31, 32]. The cingulate gyrus was involved in visceral stimulation and the urge to void was considered as a nonpainful visceral stimulation [11]. As mentioned, the anterior or median cingulate cortex controls the heart rate via sympathetic mechanisms [33, 34]. The dorsal anterior or median cingulate cortex was speculated to control the lower urinary tract via the same mechanism, which cannot be precisely identified now. Under a strong desire to void or urgency, the activated dorsal anterior cingulate cortex would facilitate to urinary continence by urinary sphincter contraction and bladder relaxation [35]. In our study, we detected an increased E_{nodal} in right median cingulate gyrus under the strong desire to void.

Pelvic floor muscles which are important in stress urinary incontinence cannot be isolated. In the male group, supplementary motor area (SMA), an adjacent location to dorsal anterior cingulate cortex, showed the increased E_{nodal} under the strong desire to void. In previous researches, SMA showed the activated response during the pelvic floor muscle's voluntary contraction [36, 37]. Yin et al. demonstrated that the middle temporal gyrus and the right inferior frontal gyrus inhibited detrusor contraction together during urinary bladder storage in healthy subjects [38]. Patients with detrusor overactivity were found weaker in the two regions [36]. Besides Cohen and coworker [39] suggested that the cingulate gyrus and premotor cortex played important roles in the regulating selective attention under task-conflict condition. During the research, these subjects who had the strong desire to void knew voiding in the scanner was inappropriate.

Visceral perception, including urinary bladder filling sensory, can be integrated with exteroceptive and interoceptive signals [14]. The frontal operculum is a region adjacent to the insula, which involves the awareness and processing of interoceptive signals [37]. The supramarginal gyrus, located in the inferior parietal lobe (IPL), showed a crucial association with proprioception. A recent study has suggested that the regions were activated under the condition of visceral perception, such as heartbeat [40]. The Multifunction of IPL has been revealed in multisensory integration, spatial attention, higher cognitive functions, and oculomotor control [41, 42]. An earlier PET and fMRI study showed the IPL also responds to urinary bladder cooling during the bladder storage using ice water [13–43]. Meanwhile, the human fusiform gyrus is a region concerning objects recognizing and functional definition, which often interacts

with the occipital lobe on visual tasks [44]. The occipital cortex change has been mentioned in previous researches, but the mechanism was not systematically discussed [45, 46].

Distinctly, regional E_{nodal} in the male group's thalamus was decreased under a strong desire to void state. No difference was observed between urinary bladder filling and emptying in the female group. As a relay station, the thalamus transmits the sensory signals from PAG to the insula, lateral PFC and medial PFC in terms of a frame established via several animal and human researches [9, 47]. Decreased E_{nodal} in thalamus suggesting the lower efficiency in information transmission in regionally connected graphs. The study of Kuhtz-Buschbeck et al [35] had similar gender differences, in which thalamus in healthy males was less activated under the urge to void compared with healthy females. But the activity in other brain regions under the both urinary bladder states were not compared in detail. In our study, compared with the empty urinary bladder state, the more regions of PFC in female group showed the increased E_{nodal} under a strong desire to void state. SMA as the motor control was significantly with the increased E_{nodal} in the male group but not in the female group. Gehring and Knight [48] had suggested the activation in premotor cortex worked with the cingulate gyrus to monitor behavior and guiding compensatory system, the gender difference may partly result from the compensatory system. Under a strong desire to void, subjects' brain monitored and regarded that the voiding in the scanner was inappropriate, the pelvic floor muscle contraction might be initiated as a compensatory mechanism to resist urine leakage.

No consensus has been reached in gender differences in central LUT control. Compared with female genitourinary system, the male longer urethra and prostate may impact on the brain response for the desire to void with or without the catheters. Blok and his coworkers [49] had indicated that different level of activation in the insula, hypothalamus and PAG during micturition and urine withholding between healthy female and males in his PET study. A meta-analysis of neuroimaging studies has revealed that activated clusters in brainstem (periaqueductal gray and rostral pons), thalamus, insula, and cerebellum to response the urinary bladder filling and no significant difference in brain activation between female and male subjects was detected [50]. Although only cortical and subcortical regions without pons and cerebellum were involved in our study, its results have provided the evidence for gender difference in responses to the strong desire to void under the pattern.

Finally, the sample size was small, which may be a potential limitation of the study. On the other hand, due to the AAL atlas we used to define the regions of interest, only brain activity in cortical and subcortical regions were in focus. We will consider the future studies covering the cerebellum and pons to obtain more integrated information.

5. Conclusions

With the repetitive infusion and withdrawal pattern, we detected different functional topologic property alternations of the healthy female and male subjects between the strong desire to void and empty

bladder state in our study. The baseline findings in healthy females and males might help understand the underlying pathogenesis in LUTD patients during the urodynamic tests.

Abbreviations

fMRI functional magnetic resonance imaging

AAL Automated anatomical labeling

LUTD lower urinary tract dysfunctions

LUT lower urinary tract

E_{glob} global efficiency

E_{loc} local efficiency

L_p characteristic path length

C_p clustering coefficient

E_{nodal} nodal efficiency

PAG periaqueductal gray

PFC prefrontal cortex

PET positron-emission tomography

SPECT single photon emission computed tomography

DMN default mode network

SMA supplementary motor area

IPL inferior parietal lobe

Declarations

Ethics approval and consent to participate

We got the ethics approval from Ethics Committee of China Rehabilitation Research Centre (address, No 10. Jiaomen Beilu, Fengtai District, Beijing 100068, China; the chief of the ethics committee, Jingjie He; IRB: 2017-002-1; Approval date, 2017/02/07). We have gotten consent form from all the participants in the study.

Consent for publication

Xiaoqian Ying, Yi Gao and Limin Liao consented for the publication.

Competing Interest: There is no conflict of interest.

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Contribution Details:

-	Xiaoqian Ying	Yi Gao	Limin Liao
Concepts			√
Design		√	√
Definition of intellectual content			√
Literature search	√	√	
Clinical studies	√		
Experimental studies			
Data acquisition	√	√	
Data analysis	√		√
Statistical analysis	√	√	√
Manuscript preparation	√	√	
Manuscript editing	√	√	
Manuscript review			√
Guarantor			√

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Availability of data and materials

The datasets used during the current study are available from the corresponding author on reasonable request.

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Figures

Figure 1

The characteristics of the healthy female and male subjects.

Figure 2

Brain functional connection matrix of healthy female and male subjects under the both of states.

Figure 3

Urodynamic findings showed the stationary and normal urinary storage in all healthy subjects.

Figure 4

The Cp, Lp, Eg and Eloc in healthy female subjects between the both of states. Legend: It showed that the significantly increased Cp, Lp, Eglob and decreased Eloc in these females. Cp, clustering coefficient ;Lp, characteristic path length; Eglob, global efficiency; Eloc, local efficiency ($P \leq 0.05$).

Figure 5

The Cp, Lp, Eg and Eloc in healthy male subjects between the both of states. Legend: It showed that the significantly decreased Cp in the female subjects, without significant changes in Cp Lp, Eglob. Cp, clustering coefficient ;Lp, characteristic path length; Eg, global efficiency; Eloc, local efficiency ($P \leq 0.05$).

Figure 6

The brain regions with an alternated Enodal in the healthy male subjects between the both of states. Legend: (a) For female subjects, a larger Enodal in bilateral calcarine fissure and surrounding cortex, lingual gyrus, and fusiform gyrus under empty bladder state. (b) Under the strong desire to void, a larger Enodal in left inferior frontal gyrus and the orbital part of middle frontal gyrus, right median cingulate, middle occipital gyrus and middle temporal gyrus, and bilateral gyrus rectus, inferior parietal gyrus and supramarginal gyrus was detected in healthy females. (c) The larger Enodal in right inferior occipital gyrus and thalamus of male subjects under empty bladder state. (d) The significant increased Enodal of healthy male subjects presented in right frontal operculum and medial superior frontal gyrus, left supplementary motor area and the bilateral supramarginal gyrus ($P \leq 0.05$).